Development of the nocturnal sleep electroencephalogram in human infants

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Development of the nocturnal sleep electroencephalogram in human infants. Am J Physiol Regul Integr Comp Physiol 286: R528–R538, 2004. First published November 20, 2003; 10.1152/ajpregu.00503.2003.—The development of nocturnal sleep and the sleep electroencephalogram (EEG) was investigated in a longitudinal study during infancy. All-night polysomnographic recordings were obtained at home at 2 wk and at 2, 4, 6, and 9 mo after birth (analysis of 7 infants). Total sleep time and the percentage of quiet sleep or non-rapid eye movement sleep (QS/NREMS) increased with age, whereas the percentage of active sleep or rapid eye movement sleep (AS/REMS) decreased. Spectral power of the sleep EEG was higher in QS/NREMS than in AS/REMS over a large part of the 0.75- to 25-Hz frequency range. In both QS/NREMS and AS/REMS, EEG power increased with age in the frequency range <10 Hz and >17 Hz. The largest rise occurred between 2 and 6 mo. A salient feature of the QS/NREMS spectrum was the emergence of a peak in the sigma band (12–14 Hz) at 2 mo that corresponded to the appearance of sleep spindles. Between 2 and 9 mo, low-frequency delta activity (0.75–1.75 Hz) showed an alternating pattern with a high level occurring in every other QS/NREMS episode. At 6 mo, sigma activity showed a similar pattern. In contrast, theta activity (6.5–9 Hz) exhibited a monotonic decline over consecutive QS/NREMS episodes, a trend that at 9 mo could be closely approximated by an exponential function. The results suggest that 1) EEG markers of sleep homeostasis appear in the first postnatal months, and 2) sleep homeostasis goes through a period of maturation. Theta activity and not delta activity seems to reflect the dissipation of sleep propensity during infancy.

SLEEP SHOWS DRAMATIC CHANGES ACROSS EARLY DEVELOPMENT.
Quiet sleep or non-rapid eye movement sleep (QS/NREMS) increases in the course of the first year after birth, whereas active sleep or rapid eye movement sleep (AS/REMS) decreases (38, 41, 50). Several groups demonstrated that slow wave sleep (SWS, stages 3 and 4 of NREMS) becomes predominant in the first part of the night from age of 2 to 5 mo onward (6, 7, 12, 21). On the basis of these observations, a number of authors postulated developmental, functional, and regulatory processes of sleep during ontogeny (7, 41, 50, 51). Roffwarg and colleagues (50) were the first to propose that AS, regulatory processes of sleep during ontogeny (7, 41, 50, 51). Salzarulo and Fagiolli (51) suggested an early appearance of sleep regulatory mechanisms. They based their hypothesis on the temporal structure of infant sleep, which is characterized by a higher level of SWS early at night than late at night, a pattern that may reflect the nocturnal dissipation of sleep propensity (7).

The majority of previous studies during ontogeny focused on the quality of sleep, on the percentage and temporal organization of sleep states, and on sleep cycles (6, 7, 12, 31, 35, 38, 41, 50). In studies of adult sleep, quantitative measures of the electroencephalogram (EEG), such as spectral power, have been increasingly used to investigate sleep regulatory processes (1, 9). It was shown that specific facets of the EEG can serve as a marker of a sleep process (9). Slow-wave activity (SWA, power in the 0.75- to 4.5-Hz range) or delta activity was used to delineate a homeostatic process (Process S) in the framework of the two-process model of sleep regulation (8, 13). SWA declines in the course of sleep, and its level in the first NREMS episode is determined by the duration of prior wakefulness. Based on these dynamics, SWA was used to delineate the time course of Process S.

Prechtl (46) was among the first to apply spectral analysis of the sleep EEG in human infants. Over the past 30 yr, a number of authors have computed power spectra in infants and have contributed to the knowledge about quantitative characteristics of the sleep EEG during development (29, 30, 42, 52–55, 58). While some reports were based on short daytime recordings (30, 55), others focused on the newborn or preterm age period (29, 30, 42, 54). The development of sleep regulation in early ontogeny, however, was not a major focus of these studies. The aim of the present longitudinal study in human infants was to document state-related and frequency-dependent changes of the sleep EEG. In particular, those facets of the sleep EEG were studied which are markers of the homeostatic process in adults. To obtain a complete picture of sleep regulation, continuous 24-h recordings would have been required. For practical reasons, the experiments had to be limited to the nocturnal period.

METHODS

Subjects

Eleven healthy full-term infants (5 boys and 6 girls) were recruited from the Department of Gynecology and Obstetrics at the University Hospital of Zurich (Switzerland) and through private sources. Birth weight ranged from 2,890 to 4,230 g (mean ± SE was 3,724 ± 138 g). The length at birth was between 48 and 56 cm (52.5 ± 0.6 cm) and head circumference between 34 and 37.5 cm (35.2 ± 0.4 cm). Gestational age ranged from 38 to 42 wk (40.0 ± 0.38 wk). All infants had a normal birth process with uncomplicated postnatal adaptation. The Apgar scores at 5 min were between 7 and 10 (9.0 ± 0.26). At birth physical examination was normal. All infants were fully breast-fed up to 2 (n = 1) or 6 (n = 10) mo after birth. Written informed consent was obtained from the parents.

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consent was obtained from all parents after detailed explanation of the method and aim of the study. The procedures were approved by the ethical committee of the University Children’s Hospital Zurich (Switzerland), and the study was performed according to the Declaration of Helsinki.

Polysonmographic Recording Procedures

All-night home polysomnography was carried out longitudinally at 2 wk (17.9 ± 1.3 days) and at 2 (69.1 ± 2.2 days), 4 (133.8 ± 2.2 days), 6 (187.9 ± 2.5 days), and 9 (282.0 ± 2.9 days) mo after birth. The EEG, submental electromyogram (EMG), electro-oculogram (EOG, differential recording), electrocardiogram (ECG), and respiratory movements (using a thoracic respiration belt, Velcro Tab; Newlife Technologies, Midlothian, VA) were recorded with a portable polygraphic amplifier system (PS1; Institute of Pharmacology and Toxicology, University of Zurich, Switzerland). The signals were digitized and transmitted via fiber-optic cable to a portable computer unit with a signal processor board. EEG, EOG, and EMG signals were conditioned by two analog filters: a high-pass filter (~3 dB at 0.16 Hz) and a low-pass filter (~3 dB at 70 Hz, less than ~28 dB at 256 Hz). The data were sampled with a frequency of 512 Hz, digitally filtered (EEG and EOG: low-pass filter at 30 Hz; EMG: band-pass filter between 20 and 50 Hz), and stored on hard disk with a resolution of 128 Hz.

The recordings were performed at home in the habitual sleep environment with usual bedtime routines and were unattended during the night. The parents were contacted by phone before each recording session to obtain information on the health status and sleep-wake rhythms during the preceding days. No infant received medication before and during the recordings. All infants were free of any infectious or respiratory diseases at the time of recording and had regular sleep-wake schedules. The experimenter (Jenni) attached the electrodes in the early evening between 1800 and 2100 before the usual bedtime. Occasionally, infants fell asleep during this procedure. EEG electrodes were placed along the antero-posterior axis over both hemispheres (bipolar derivations: F3/C3, F4/C4, C3/P3, C4/P4, P3/O1, P4/O2; referential derivation: C3/A2) according to the International 10–20 System. Grass EC-2 electrode paste (Grass Instrument Division, West Warwick, RI) was used for the application of EEG and EOG gold electrodes. Self-adhesive silver-silver-chloride electrodes were used for EMG and ECG. The electrodes were secured with a tubular elastic net bandage.

Data are means ± SE. Data derived from visual scoring (based on referential derivation C3/A2). The first 418.7 min of total recording time (TRT) were analyzed (n = 7, see METHODS for details). TST, total sleep time; SEF, sleep efficiency (TST as % TRT); WASO, waking after sleep onset; IS, indeterminate sleep; QS/NREMS, quiet sleep or non-rapid eye movement sleep; AS/REMS, active sleep or rapid eye movement sleep; MT, movement time. Nonparametric Friedman 2-way ANOVA for age trends and Wilcoxon signed rank tests for between-group differences were performed; † or ‡ indicates significant increase or decrease between successive episodes (P < 0.05), whereas * or †† indicates a trend (P < 0.01). NS, nonsignificant, NA, not applicable.

Table 1. Sleep stage and cycle variables in human infants across the first 9 mo of life

<table>
<thead>
<tr>
<th>Age</th>
<th>2 wk</th>
<th>2 mo</th>
<th>4 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>F(4,52) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRT, min</td>
<td>627.9±35.1</td>
<td>609.6±23.5</td>
<td>623.9±20.3</td>
<td>638.7±25.9</td>
<td>632.6 (43.1)</td>
<td>NS</td>
</tr>
<tr>
<td>TST of first 418.7 min TRT, min</td>
<td>312.6±9.0</td>
<td>333.4±15.2</td>
<td>365.2±11.2</td>
<td>377.1±9.7</td>
<td>377.6±6.3</td>
<td>3.4 (&lt;0.01)</td>
</tr>
<tr>
<td>SEF, %</td>
<td>74.7±2.2</td>
<td>79.6±3.6</td>
<td>87.2±2.7</td>
<td>90.1±2.3</td>
<td>90.2±1.5</td>
<td>3.4 (&lt;0.01)</td>
</tr>
<tr>
<td>WASO, %</td>
<td>21.2±2.7</td>
<td>16.2±2.4</td>
<td>10.4±2.9</td>
<td>8.3±2.2</td>
<td>8.0±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>QS/NREMS, %</td>
<td>36.7±3.2</td>
<td>45.2±1.7</td>
<td>64.1±1.3</td>
<td>65.8±1.1</td>
<td>70.0±1.4</td>
<td>34.4 (&lt;0.001)</td>
</tr>
<tr>
<td>IS, %</td>
<td>9.8±1.0*</td>
<td>7.0±0.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>AS/NREMS, %</td>
<td>51.5±3.6</td>
<td>47.6±1.8</td>
<td>35.9±1.3</td>
<td>34.2±1.1†</td>
<td>30.0±1.4</td>
<td>18.6 (&lt;0.001)</td>
</tr>
<tr>
<td>MT, min</td>
<td>17.4±3.2</td>
<td>17.6±2.8</td>
<td>10.0±1.8</td>
<td>7.0±1.0</td>
<td>7.6±0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Sleep Stage Scoring

Following generally accepted procedures, scoring of sleep stages was performed according to Anders and coworkers (5) at age 2 wk and 2 mo, while subsequent recordings were scored according to Guilleminault and Soquet (28). The latter scoring rules take into account that spindles and slow waves are present in older infants and therefore allow to differentiate between stage 1 sleep (S1), stage 2 sleep (S2), and SWS. Thus the scoring criteria resemble those used in adults (48). Sleep was visually scored (referential derivation C3/A2) for consecutive 20-s epochs as QS in younger infants (<4 mo) or NREMS in older infants (>4 mo) and as AS in younger infants (<4 mo) or REMS in older infants (>4 mo). Indeterminate sleep (IS) was scored only at 2 wk and 2 mo. In older infants, NREMS was subdivided into S1, S2, and SWS. The criterion for the latter was a peak-to-peak value of 75 μV of slow waves. EEG power in the low delta (0.75–1.75 Hz) and sigma (12–14 Hz) band was displayed on the computer monitor together with the raw data to facilitate the scoring procedure.

Sleep Cycle

A sleep cycle was defined as the succession of a QS/NREMS episode lasting at least 15 min and an AS/REMS episode of at least 5 min duration (adapted from Ref. 22). For the first AS/REMS episode no minimum criterion was applied. Sleep-onset AS/NREMS was not considered to be the beginning of a sleep cycle, although it was regularly seen in younger infants. Sleep episodes were terminated when >10 min of IS or wakefulness occurred. IS occurring at the transition from QS to AS terminated the QS episode and was considered to be part of the subsequent AS episode; IS at the transition from
AS to QS was included in the subsequent QS episodes. At least five QS/NREMS-AS/REMS cycles (n = 7 infants) were completed with the exception of infants at age 2 wk (who completed at least 3 cycles) and 6 mo (only 6 infants completed 5 cycles).

Spectral Analysis of the EEG

From seven infants, complete longitudinal recordings were obtained at all ages (bipolar EEG derivation C4P4; subject nos. 01, 02, 05, and 07 were excluded because of artifacts or detachment of electrodes). The C4P4 derivation was selected on the basis of the maximal amount of artifact-free data that were available. Power spectra of consecutive 20-s epochs (Fast-Fourier Transform routine, Hanning window, averages of five 4-s epochs) were computed, resulting in a frequency resolution of 0.25 Hz. The lowest two frequency bins (0.25 and 0.5 Hz) were not used for analysis because of their sensitivity to artifacts (in particular, sweating artifacts during AS/REMS). Artifacts were excluded by visual inspection and semi-automatically based on low-frequency and high-frequency EEG power. Only 20-s epochs without artifacts were used for analysis. Spectral data were analyzed up to 25 Hz. Spectra of 20-s epochs were matched with the corresponding sleep stages. Average power spectra (see Figs. 1 and 2) were based on the first 272 min (maximal common sleep time, uncontaminated data devoid of ECG or sweating artifacts), and on the first four cycles (see Fig. 6). The time course of selected frequency bands (see Figs. 4 and 5) was based on the available cycles (statistics restricted to number of cycles available in all infants; see legends for details).

Statistics

Statistical analysis was performed using the SAS statistical software package (SAS Institute, Cary, NC). Age trends of visually scored sleep and cycle variables were assessed by nonparametric Friedman two-way ANOVAs and within-age-group effects by Wilcoxon signed rank tests. Absolute EEG power density measures were analyzed by one-way or two-way ANOVAs for repeated measures (rANOVA). Absolute power values were log-transformed before statistical tests to approximate a normal distribution. Probability values are based on Greenhouse-Geisser corrected degrees of freedom, but the original degrees of freedom are reported. The significance level was set at P < 0.05. Post hoc comparisons between and within age groups were performed by paired t-tests if the corresponding main factor or the interaction of the rANOVA was significant.

The mean time course of power in a selected frequency range was calculated by subdividing each QS/NREMS episode into seven equal intervals and each AS/REMS episode into three equal intervals. For each interval, mean power was calculated for subjects and then averaged across subjects. Statistics were based on mean power per QS/NREMS and AS/REMS episode. A one-way rANOVA with factor “episode” (QS/NREMS episodes 1–5 or AS/REMS episodes 1–5, except for age 2 wk with episodes 1–3 only) served to analyze the dynamics in the course of the night. If the rANOVA revealed a significant effect of episode, consecutive episodes were compared by two-tailed paired t-tests. Only complete cycles were analyzed. Incomplete cycles or wakefulness between completed cycles gave rise to gaps in the average curves. Completed cycles were plotted with respect to the average time of occurrence. A gap in the plot was introduced whenever the interval between successive cycles was larger than 18 min (~3 times the average subdivision of an episode).

RESULTS

Sleep Stage and Cycle Variables Derived from Visual Scoring

Table 1 shows mean values of visually scored sleep variables for each age group. TRT varied considerably among subjects and age groups. Therefore, the maximum common length of TRT of 418.7 min was analyzed. Total sleep time (TST) and sleep efficiency increased from 2 wk to 6 mo of age, whereas movement time and waking after sleep onset decreased. However, the decline of the latter did not reach statistical significance. AS/REMS expressed as percentage of TST showed a marked decline during maturation, whereas QS/NREMS increased between 2 wk and 4 mo and stabilized thereafter.

The mean duration of the sleep cycle (53–64 min) showed no age-related variation, whereas the proportion of its two constituent sleep episodes changed in an opposite direction: QS/NREMS episodes increased and AS/REMS episodes decreased.

EEG Power Spectra of QS/NREMS and AS/REMS

Spectral power of the sleep EEG (Fig. 1A) showed the typical decline with increasing frequency that is well documented for adult sleep (10). A striking developmental change in the QS/NREMS spectrum was the emergence of a peak in the frequency range of sleep spindles (12–14 Hz). The peak appeared at the age of 2 mo and was present in each individual spectrum. Visual inspection of the EEG revealed that the spectral peak coincided with the emergence of sleep spindles. rANOVA showed significant effects of “state,” “age,” and their interaction over almost the entire frequency range (Fig. 1B, bottom). High F-values were present in the upper delta band for age and in the low delta, theta, alpha, sigma, and low beta band for state.

To visualize state-related differences, the spectral values of QS/NREMS were plotted relative to those of AS/REMS (Fig. 1B). In newborns, power in QS exceeded power in AS in the range of 1 to 15.5 Hz. Also in older infants, power in the low delta band remained higher in QS/NREMS than in AS/REMS. However, some differences between the states were no longer significant in the high delta (2–9 mo) and low theta (2–4 mo) band. Based on these findings, we decided to analyze power specifically in the frequency range of 0.75–1.75 Hz (low delta activity) rather than in the more extended range referred to as SWA (0.75–4.5 Hz). The largest state-related differences were present in the spindle frequency range, where power in QS/NREMS exceeded power in AS/REMS by a factor of four to six.

The age-related changes in QS/NREMS and AS/REMS are visualized in Fig. 2. Power over the entire frequency range is expressed for each age relative to power at 2 wk. Although the values increased with age almost over the entire frequency range in both sleep states, the largest rise in power was seen in the delta band. Close to maximal levels of delta power were reached at 6 mo for NREMS and already at 4 mo for REMS. The emergence of the sigma peak coincident with sleep spindles is evident in the QS/NREMS spectra. Also in the beta range, a conspicuous increase in power was seen between 4 and 9 mo.

Developmental Trends in Time Course of Low Delta, Theta, and Sigma Activity

Figure 3 shows the developmental changes in the dynamics of low delta (0.75–1.75 Hz), theta (6.5–9 Hz), and sigma (11.5–13.25 Hz) activity in an individual. Power in all three
Fig. 1. Electroencephalogram (EEG) power spectra (bipolar derivation C4P4) of the first 272 min of sleep (maximum common duration of artifact-free sleep). A: absolute spectra in quiet sleep (QS)/non-rapid eye movement sleep (NREMS) (thick lines) and active sleep (AS)/rapid eye movement sleep (REMS) (thin lines). B: relative spectra (each frequency bin in QS/NREMS expressed relative to the corresponding bin in AS/REMS). Bars at bottom in each panel indicate frequency bins in which absolute power density in QS/NREMS and AS/REMS differed significantly \( P < 0.05 \); 2-tailed paired t-test, performed for frequency bins for which a 2-way repeated measures (r) ANOVA factor “state” or the interaction “age \times state” was significant, bottom right; only significant \( F \)-values (\( P < 0.05 \)) are depicted.
frequency bands showed a modulation by the QS/NREMS-AS/REMS cycle with low values in AS/REMS and high values in QS/NREMS. Whereas at 2 wk and 2 mo low delta and theta activity showed a similar time course, as a dissociation became apparent at the age of 4 mo (not shown) and thereafter. At 6 and 9 mo, theta activity exhibited a declining trend across consecutive sleep episodes. In contrast, low delta activity showed an alternating pattern with high values in every second NREMS episode. At 2 wk, sleep spindles were not yet present and, accordingly, sigma activity was at a very low level. From 2 mo onward, when sleep spindles were clearly recognized visually in QS/NREMS, sigma power exhibited high values in QS/NREMS episodes.

To examine the main features of the age-related development and dynamics in specific frequency bands, average data were computed (Fig. 4). Sleep cycles were standardized by subdividing QS/NREMS episodes into seven equal time intervals and AS/REMS episodes into three intervals; next, the data were averaged across subjects. Instead of showing the typical alternation of high and low delta activity, one subject (no. 09) exhibited high power in NREMS episodes 1, 4, and 8 at 6 mo and in episodes 1, 4, 6, and 8 at 9 mo. Waking episodes did not exceed 10 min. In view of this aberrant pattern, this subject was excluded from the analyses at 6 and 9 mo shown in Fig. 4 and Fig. 6 (n = 6).

Dynamics of low delta activity. At 2 wk, a uniform picture with high values in QS and low values in AS was seen. From 2 mo onward, an alternating pattern of high-level and low-level delta activity emerged. There was no conspicuous global decline of low delta activity in the course of the night. At 6 mo, the difference in power between consecutive NREMS episodes was largest. At 9 mo, the alternating pattern was restricted to the first four cycles. The values in AS/REMS episodes were invariable at a low level, and no trend was apparent (Fig. 4).

At the beginning of a QS episode, low delta activity showed a steep rise at 2 wk and 2 mo. At later ages the intraepisodic build-up became more gradual. Low delta activity showed a steep decline before the onset of AS/REMS (in particular in episodes with high levels of low delta activity). The first data point in all panels of Fig. 4 does not correspond to sleep onset, since at this age AS/REMS occurred regularly at sleep onset. By definition, cycles started with QS/NREMS; therefore, sleep onset AS/REMS was not included in the first cycle (see Methods). As the occurrence of sleep-onset AS/REMS and of interrupted cycles at the beginning of the sleep episode decreased with age, the first data point was advanced.

Dynamics of theta activity. At 2 wk, the time course of theta activity resembled that of low delta activity. At 2 mo, theta activity was highest in the first QS episode and then was at a uniform lower level in the following QS episodes. At 4 mo, a gradual decline of theta activity across NREMS episodes emerged, a trend that was most pronounced at 9 mo. In contrast to low delta activity, theta activity showed a decline across REMS episodes in the early part of the sleep episode.

The decline of theta activity across NREMS episodes at 9 mo is plotted for individual standardized values in Fig. 5. An exponential function (for equation see legend of Fig. 5) was fitted to the data. Its time constant (τ) was 81.3 min (SE 13.2 min), the asymptote (TAα) 69.2% (4.6%), and the initial value minus the asymptote (TAα) 169.3% (12.1%). The asymptotic r² of 0.81 indicated a good fit.

Dynamics of sigma activity. Sigma peak frequency changed with age and sleep cycle. The peak frequency within the sigma band was determined individually for each mean spectrum. The peak frequency increased from 12.6 Hz (SE 0.05) at 2 mo to 13.1 Hz (0.14) at 9 mo (rANOVA factor age, P < 0.05). Individual 1.25-Hz bands in the sigma range were defined around the individual peak frequency (midbin; range of 1.25-Hz sigma bands from 11.5 to 13.5 Hz).

From age 2 mo onward, sigma activity was observed in all QS/NREMS episodes. At 6 mo, when the alternating pattern of low delta activity was most prominent, sigma power showed a parallel, though less pronounced, alternating pattern (Fig. 4). A prominent feature of the intraepisodic time course was the rapid increase at QS/NREMS onset and the sharp decline before AS/REMS onset. The intraepisodic U-shape of sigma activity reported in adults (2, 61) was absent, and there was no increase in the course of the night.

Evolution of EEG Spectra in the First Four Episodes

Figure 6 depicts the evolution of power in the first four episodes of QS/NREMS and AS/REMS. Power in episodes 2 to 4 was expressed relative to the first episode.

At age 2 wk, neither QS nor AS showed significant changes across episodes. Consistent significant variations appeared in QS at 2 mo and in REMS at 4 mo.

The pattern in QS/NREMS (age 2–9 mo) was characterized by a progressive decline of power in the theta and alpha range. This was not the case in the low delta band, where the alternating pattern was reflected by lower values in episode 2 than in episode 3. With advancing age, the frequency delimit-
ing the alternating pattern shifted from 2.7 Hz at 2 mo to 5 Hz at 9 mo. At age 6 and 9 mo, power in the sigma range exhibited an alternating pattern with lower values in episode 2 than in episode 3. However, statistically significant variations in the sigma range occurred only at 6 mo.

In AS/REMS, the significant changes were restricted to a narrower frequency range than in QS/NREMS and encompassed consistently the theta, alpha, and beta range. In this frequency range, a decrease of power occurred from the first to the second AS/REMS episode, whereas beyond the second AS/REMS episode the decreasing trend was less evident. The difference between the first and the following REM episodes was largest at 9 mo.

DISCUSSION

In this longitudinal study, the sleep of infants was recorded in the home environment at different stages of development within the first postnatal year. This allowed specification of maturational changes of the sleep EEG and its dynamics across the sleep episode.

Sleep Architecture

A conspicuous change in sleep architecture from the age of 2 wk to 9 mo was the decreasing percentage of AS/REMS and the complementary rise in the percentage of QS/NREMS. The altered proportion of the two sleep states came about by the shortening of AS/REMS episodes and the lengthening of QS/NREMS episodes, whereas the sleep cycle remained stable at ~60 min. Similar age-related changes in sleep states have been reported previously (12, 19, 31, 38, 50). With the exception of a single study (23), a stable sleep cycle duration during infancy was observed in earlier studies (19, 21, 38, 59). However, it is still unknown at which age the adult cycle length of 90–110 min is attained. Whereas the cycle duration of 75 min (38) at the age of 2 yr was reported to increase to ~90 min at 6 yr (11), data in the intervening years are not available. On the basis of the presence of SWS in alternate QS/NREMS episodes, Bes and colleagues (7) proposed that the recurrence time of SWS in infants is similar to that in adults, indicating that the ultradian component of SWS in infants already represents the adult sleep cycle.

Sleep EEG

A central feature of the present study was the use of quantitative EEG analysis, which complemented the conventional scoring of sleep states. The prominent rise in spectral power within the first 6 mo is in agreement with previous findings (58). The largest increase in power was present in the low-frequency range of the spectrum (Fig. 2). Because the
changes were similar in QS/NREMS and AS/REMS, they may represent a sleep state-independent aspect of EEG development. The EEG reflects changes in postsynaptic potentials of large and distributed neuronal populations (37). The degree of synchronization of these postsynaptic potentials is reflected in the amplitude of the scalp-recorded EEG signal (37). Thus the marked state-independent increase of EEG power during early infancy may reflect an increase in synaptic connectivity of neuronal assemblies (32), developmental changes in neurotransmitter or neuroreceptor properties (36), and the increasing

![Diagram of EEG power in different age groups](http://ajpregu.physiology.org/)

**Fig. 4.** Average time course of low delta activity (A, EEG power in the 0.75- to 1.75-Hz range), theta activity (B, 6.5–9 Hz) and sigma activity (C) in each age group (2 wk, 2 and 4 mo, n = 7; 6 and 9 mo, n = 6). Because the peak frequency of the sigma range in mean spectra changed as a function of age and varied considerably among subjects and cycles, individual 1.25-Hz bands were defined with the peak frequency as the midbin (range 11.5–13.5 Hz). QS/NREMS episodes were subdivided into 7 and AS/REMS episodes into 3 equal time intervals and averaged across subjects. Vertical lines represent ± 1 SE. Black bars and dotted vertical lines delimit AS/REMS episodes. Filled triangles above the abscissas represent QS/NREMS and AS/REMS episodes for which the mean power of the episode differed significantly from the following episode (P < 0.05, 2-tailed paired t-test). The orientation of triangles specifies the direction of difference between indicated and consecutive episode. Open triangles represent a trend (P < 0.1). t-Tests were only performed when a 1-way rANOVA with factor “episode” revealed a significant effect of episode (P < 0.05, indicated in top right in each panel) over the first 5 episodes (first 3 episodes at 2 wk). Only completed sleep cycles were included. 2 wk: Cycles 1–3, n = 7 and cycle 4, n = 6; 2 mo: cycles 1–6, n = 7; 4 mo: cycles 1–6, n = 7 and cycle 7, n = 6; 6 mo: cycles 1–7, n = 6; 9 mo: cycles 1–5, n = 6 and cycles 6–7, n = 5. The first data point does not correspond to sleep onset, since in younger age AS/REMS was regularly seen at sleep onset, but was not included in the first cycle (see methods).
Daytime sleep was found to decrease during infancy from 4.6 h sleep EEG during the night. For a thorough analysis of sleep EEG dynamics and sleep homeostasis development and integrity of the central nervous system in Thalamocortical neurons and their synaptic interactions (14, 56, synchronous oscillations within the thalamocortical system, period from the fetal to the infant state, which occurs during emergence of spindles may be part of the functional transition as a measure of low-frequency EEG activity. The prominent peak between 12 and 14 Hz emerging in the spectral power density of the sleep EEG has been consistently demonstrated for sleep stages NREM1 and NREM2 in adults, and it is also present in infants during the first days of life. However, the characteristics of sleep spindles in infants differ from those in adults. The frequency of sleep spindles is lower in infants, and the duration of individual sleep spindles is shorter. Moreover, sleep spindles in infants are more likely to be isolated rather than occurring in clusters, as is typical in adults.

The prominent peak between 12 and 14 Hz emerging in the QS spectrum at 2 mo coincided with the appearance of sleep spindles. A close association of sleep spindles and the sigma frequency of the delta band, power in QS/NREMS and AS/REMS did not differ significantly (Fig. 1). This pattern is not present in the adult sleep EEG (10) and may indicate functional differences of distinct parts of the delta band during development. Therefore, instead of relying on the traditional SWA (0.75–4.5 Hz), the frequency range of 0.75–1.75 Hz was used as a measure of low-frequency EEG activity.

The prominent peak between 12 and 14 Hz emerging in the QS spectrum at 2 mo coincided with the appearance of sleep spindles. The prominence of sleep spindles in the frequency spectrum is closely related to the development of myelination of the brain’s white matter, which is known to occur during the first year of life.

The EEG spectra of QS/NREMS and AS/REMS differed already at the age of 2 wk (Fig. 1). Between 1 and 16 Hz, power in QS was higher than in AS. State-related differences within the delta band were limited at the age of 2 mo and older to the lowest frequencies. Within the middle or higher frequencies of the delta band, power in QS/NREMS and AS/REMS did not differ significantly (Fig. 1). This pattern is not present in the adult sleep EEG (10) and may indicate functional differences of distinct parts of the delta band during development. Therefore, instead of relying on the traditional SWA (0.75–4.5 Hz), the frequency range of 0.75–1.75 Hz was used as a measure of low-frequency EEG activity.

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decay of theta power at 9 mo is inferior to that of delta activity in adults (81.3 vs. 144.6 min; see Ref. 15). Based on findings in rat pups (4), it is not unreasonable to assume that the build-up and dissipation of sleep propensity occurs faster during early development. In fact, animal models may give some insights into the ontogeny of sleep regulation (4, 25, 27).

It was shown on the basis of sleep deprivation experiments that in rat pups homeostatic sleep regulation is evident as early as the first postnatal weeks (4, 27). Although neonatal rats compensated sleep deprivation with increased time spent in QS, the waking-dependent response of delta activity occurred only later in development (27). Whether similar developmental features of homeostatic sleep regulation are present also in human infants remains unknown.

In adults, EEG sigma activity, a correlate of sleep spindles, shows in many respects an inverse relationship to delta activity. It increases over consecutive NREMS episodes and exhibits a U-shaped time course within episodes (2, 17, 61). These adult features of sigma activity were not observed during early development. At 6 mo, both low-frequency delta and sigma...
activity occurred in alternate episodes (Fig. 4). The coupling of delta and sigma activity is in accordance with electrophysiological data (56, 57) that demonstrate a close relationship between slow waves and sleep spindles. Visual inspection of the data confirmed a particular morphology of sleep spindles (spiky negative and rounded positive component) and their increasing length in the first 9 mo after birth (34, 38, 60).

Taken together, both delta activity and sleep spindles exhibit specific features during development, which may indicate a different functional role in infant and adult sleep. It is conceivable that slow waves and sleep spindles in infants promote the formation of thalamocortical networks by providing endogenous neural signals with repetitive and synchronized activity. Hitherto, AS/REMS was postulated to facilitate brain maturation by internal stimulation when sensory input is still minimal (39, 50). However, there is recent evidence that QS/NREMS in cats may consolidate changes in cortical plasticity during development, which may indicate a substates of sleep, QS/NREMS and AS/REMS, may contribute to brain development at a time period in life when the need for sleep is largest (33).

We conclude that the nocturnal pattern of specific EEG markers such as low delta, theta, and sigma activity may reflect their different functional roles in the sleep process during development. Research protocols in which sleep and wakefulness are manipulated are needed to further investigate the development of sleep regulatory processes and to gain insights into the functional role of specific frequency components in the sleep EEG during ontogeny.

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